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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,773	10/07/2003	Hajime Matsuzaki	3522.2	7374

22886 7590 02/03/2006

AFFYMETRIX, INC
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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/681,773	MATSUZAKI ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *5-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 5-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/28/2005.

Specification

2. The attempt to incorporate subject matter into this application by reference to dbSNP, Build 116, August 2, 2003 is ineffective because the reference document is not clearly identified. Firstly, it is unclear what specific information for each entry is being incorporated by reference. It is unclear if the specific sequence submitted is being incorporated by reference, or if the incorporation by reference is meant to designate disclosure of Accession numbers, PUBMED references, etc. Further, it appears that build 116 was not available until August 7, 2003, as per NCBI at nlm.nih.gov/SNP/buildhistory.cgi.. The following site: ncbi.nlm.nih.gov/mailman/htdig/dbsnp-announce/2003q3/000044.html, indicates that that ftp data, entrez indexing, and BLAST database for build 116 was not available until August 11, 2003. It is unclear from the disclosure in the specification, as to what was available August 2, 2003, and what information from the database is being incorporated by reference into the specification.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

The claims are drawn to an array comprising a plurality of nucleic acid probes wherein the array comprises each of the sequences listed in SEQ ID NOS 1-124,031. The claims are further drawn to an array comprising the complements of each SEQ ID NO:, as well as probes in which one of the sequences listed in SEQ ID NOS 1-124,031 has a mismatch at the central position.

The specification teaches that the sequences of SEQ ID NOS 1-124,031 correspond to regions of the human genome containing SNPs (single nucleotide polymorphisms) (page 22). The specification attempts to incorporate by reference the corresponding entry in dbSNP (for each SNP ID in Table 1) from build 116 dated August 2, 2005. NCBI, however, appears to indicate that build 116 was not available August 2, 2005.

The specification teaches that for each of SEQ ID NO: 1-124,031, the "disclosure" includes probes with a mismatch anywhere in the nucleic acid sequence and may comprise one or more bases (page 21, lines 6-15). It appears that the specification contemplates SNPs at any position along the disclosed SEQ ID NOS, including SNPs that have not been taught by the specification. Additionally, the claims recite probes "consisting essentially of" one of the sequences of SEQ ID NOS 1-1124,031. As the specification does not define the metes and bounds of "consisting essentially of", the recitation is considered "open" ie: comprising, as the specification does not define what is "essential" to the claimed nucleic acids along with the recited SEQ ID NOs. Therefore, the claims also again, encompass SNPS in sequences that have not been taught or described by the specification.

The specification asserts that the array can be used to " monitor loss of heterozygosity, identify imprinted genes, genotype polymorphisms, determine allele frequencies in a population, characterize biallelic markers, produce genetic maps, detect linkage disequilibrium, do association studies, analyze genetic variation, identify markers linked to a phenotype, ... compare genotypes between different individuals in a population" and forensics (page 3, pages 30-37).

The claimed nucleic acids/array are not supported by a specific asserted utility because the disclosed uses of the nucleic acids on the array are not specific and are generally applicable to any nucleic acid containing a SNP (single nucleotide polymorphism). These are non-specific uses that are applicable to nucleic acids containing SNPs in general and are not particular or specific to the nucleic acids and array being claimed.

Further, the claimed nucleic acids/array are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. While the nucleic acids may be utilized as asserted, the specification provides no association with any useful phenotype (ie pharmacogenomic association for drug metabolism), disorder, disease, relevance of SNP in any particular population, etc so that one of skill in the art would be able to use the claimed array in a real world context of use. The array can be used to search for a utility, but significant unpredictable experimentation must be undertaken to establish an association between the SNP probes and any disease, useful phenotype, etc. The need for such research clearly indicates that the products are not disclosed as to a currently available or substantial utility. The research contemplated by applicant(s) to characterize the products, does not constitute a specific and substantial utility. Identifying and studying the properties of a compound itself or the

mechanisms in which it is involved does not define a "real world" context or use. Similarly, the other listed and asserted utilities as summarized above or in the instant specification are neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the nucleic acid such that another non-asserted utility would be well established for the compounds.

There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states, as well as drug or therapeutic response. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker et al. teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789). Further, in some cases where multiple polymorphisms were identified in a gene, some of these were demonstrated to be disease associated and some were not. The unpredictability of the functionality or use of SNPs is not

limited to diagnostic uses, but is found in drug response as well. Malhotra et al (Am. J. Of Psychiatry, vol. 161, pages 780-796, May 2004) teaches that while a T102C polymorphisms in the serotonin 5-HT2A gene was reported to have a significant association with the failure to respond to clozapine in 149 patients with chronic schizophrenia, such effect was not able to be replicated in a series of subsequent studies (see page 7829 col 2). Malhotra et al teach that definitive studies in larger group sizes, prospective clinical data, and comprehensive analysis of the gene will be needed to further address the role of this gene in antipsychotic drug response (see page 783, col. 1). In the instant case, the specification only provides information that the variant exists, but provides no guidance that it has any effect whatsoever on the CYP1B1 gene, expression, or activity, let alone any potential diagnostic or therapeutic effect.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

7. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an array comprising a plurality of nucleic acid probes wherein the array comprises each of the sequences listed in SEQ ID NOS 1-124,031. The claims are further drawn to an array comprising the complements of each SEQ ID NO:, as well as probes in which one of the sequences listed in SEQ ID NOS 1-124,031 has a mismatch at the central position.

The specification teaches that the sequences of SEQ ID NOS 1-124,031 correspond to regions of the human genome containing SNPs (single nucleotide polymorphisms) (page 22). The specification attempts to incorporate by reference the corresponding entry in dbSNP (for each SNP ID in Table 1) from build 116 dated August 2, 2005. NCBI indicates, however, that build 116 was not available August 2, 2005. The specification teaches that for each of SEQ ID NO: 1-124,031, the "disclosure" includes probes with a mismatch anywhere in the nucleic acid sequence and may comprise one or more bases (page 21, lines 6-15). It appears that the specification contemplates SNPs at any position along the disclosed SEQ ID NOS, including SNPs that have not been taught by the specification. Additionally, the claims recite probes "consisting essentially of" one of the sequences of SEQ ID NOS 1-1124,031. As the specification does not define the metes and bounds of "consisting essentially of", the recitation is considered "open" ie: comprising, as the specification does not define what is "essential" to the

claimed nucleic acids along with the recited SEQ ID NOs. Therefore, the claims also again, encompass SNPS in sequences that have not been taught or described by the specification.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of nucleic acids consisting of SEQ ID NOS: 1-124,031, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it

obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over dbSNP build 115 (June 1, 2003) or build 103 (April 8, 2002), each in view of Venter (US Patent 6,812,339).

The claims are drawn to arrays comprising probes which comprise one of SEQ ID NOS 1-124,031, wherein the probes of the array comprises each of SEQ ID NOS 1-124,031. Accordingly, the array comprises at least 124,031 probes, each probe comprising one of SEQ ID

NOS 1-124,031. Claim 2 is ~~further~~ further drawn to the array comprising the complement of each of the sequences of claim 1. Claim ~~3~~ 3 is ~~further~~ further drawn to a third set of probes comprising each of SEQ ID NOS 1-124,031, except with a mismatch at the central position.

DbSNP teaches single nucleotides polymorphisms in the human genome as well as at least 30 nucleotides on the 5' end and 30 nucleotides on the 3' end of the SNP. Absent evidence to the contrary, each build listed above, is taken to provide the SNP data in each of the sequences of SEQ ID NOS 1-124,031. dbSNP does not teach providing probes comprising these SNPs on an array. However, Venter teaches that there is a need to provide arrays with allele specific probes to detect SNPs in the human genome (see abstract, col. 15 line 1- col. 16, line 14). Venter teaches that preferably, the probes should hybridize to at least about a 12, 20, 25, 40 nucleotide region (col. 14, lines 55-65), are 10, 15, 20, 25, 30, 40 etc nucleotides long (para bridging cols. 17-18), are specific to each of the variants of the allele should be included allowing for the simultaneous analysis of each possible variant on the same support (col. 15, lines 25-35), and that the preferably, the polymorphic site aligns at the central position (col. 15, lines 21-25), or 5, 4, 3, 2, or 1 nucleotides form the center of the polynucleotide (col. 18, lines 3-7). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have constructed an array of probes of 25 nucleotides, containing the SNP and corresponding allelic variants of each of the SNPs in dbSNP, because Venter teaches to provide SNP probes on an array for the purpose of detecting the variants in a sample. The ordinary artisan would have been motivated to provide array of probes containing the SNPs and alternate alleles taught in dbSNP because Venter teaches that such can be used to identify genes involved in complex disorders and enhance the selection of candidate genes most likely to contain

causative SNPs associated with a particular disease. Although Venter does not teach to provide the complement of each probe, it would have been further prima facie obvious to one of ordinary skill in the art to also provide the complement of each SNP probe to identify the appropriate SNP on either DNA strand (sense or antisense).

11. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over dbSNP Build 103 of 115, each in view of Venter as applied to claims 1-3 above, and further in view of Lough et al (US Patent 5,900,481).

The teachings of the dbSNP database in view of Venter is set forth above. The dbSNP database in view of Venter does not teach an array comprising probes specifically attached to a bead, however Lough teaches that as compared to flat surfaces, the immobilization of nucleic acids on a bead which are linked to a solid support provides for increased surface area. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use beads for immobilization of nucleic acids as taught by Lough, on the array of dbSNP database in view of Venter because however Lough teaches that as compared to flat surfaces, the immobilization of nucleic acids on a bead which are linked to a solid support provides for increased surface area.

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton
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Art Unit 1634
2/1/06